Pancreatic Society of Great Britain and Ireland

The 17th annual meeting of the Pancreatic Society of Great Britain and Ireland was held at the Postgraduate Medical Centre, Scarborough, on 20 November 1992 under the presidency of Dr Charles Mitchell. The guest lecturer was Dr Dan Longnecker who gave a presentation on 'Pancreatic cancer in transgenic mice and heterogeneous men'. The Rodney Smith Prize for the best oral presentation was awarded to Mr Mike Larvin for his paper entitled 'A prospective, multicentre, controlled, randomised trial of intraperitoneal trasylof for acute pancreatitis', and the Poster Prize was awarded to Mr C McKay for his poster on 'Monocyte production of tumour necrosis factor in acute pancreatitis is related to outcome'.

The next meeting of the Society will be held in November 1993 in London under the presidency of Mr Geoffrey Glazer.

Monocyte production of tumour necrosis factor in acute pancreatitis is related to outcome

C MCKAY, G GALLAGHER, B BROOKS, J BAXTER, C W IMRIE (University Department of Surgery, Glasgow Royal Infirmary, Glasgow) Excessive production of tumour necrosis factor alpha (TNFα) by monocytes and macrophages is widely believed to be responsible for many of the features of septic shock but its role in the pathophysiology of the systemic effects of acute pancreatitis is unknown. In an attempt to study the role of TNFα in acute pancreatitis and overcome the limitations of plasma level measurement we have studied the capacity of monocytes, isolated from 10 patients with acute pancreatitis, to secrete TNFα in vitro.

Monocytes from 10 patients with prognostically severe pancreatitis were isolated using an immunomagnetic method on the first, third, and fifth days after admission. Cells were cultured for 24 hours in serum free medium and supernatants assayed for TNFα using an in house ELISA.

There was a strong positive correlation between lipopolysaccharide induced TNFα secretion and the acute physiology score (r=0.859, p<0.01). Stimulated TNFα secretion was significantly higher in those patients with a complicated or fatal outcome (n=6, median TNFα 18.6 ng/ml/10⁶ cells, range 10.8–56) than in those with an uncomplicated course (n=4, median TNFα 4.8 ng/ml/10⁶ cells, range 4.0–8.0).

These results support the hypothesis that excessive TNFα secretion by monocytes and macrophages plays a part in the pathophysiology of the systemic effects of acute pancreatitis.

PMN-elastase as a prognostic indicator in acute pancreatitis

D FENTON-LEE, C MCKAY, A MCCLELAND, C W IMRIE (Department of Surgery, Royal Infirmary, Glasgow) In acute pancreatitis, PMN-elastase has been reported to be a useful prognostic indicator when measured within the first 24 hours of admission. We have assessed the role of PMN-elastase in a prospective series of 81 patients with a clinical diagnosis of acute pancreatitis and a serum amylase of >1000 U/l. Patients were categorised to an uncomplicated clinical course group 1 (n=63) or a complicated course group 2 (n=18). Glasgow prognostic factors and PMN-elastase were measured and correlated with clinical outcome. Patients with ≥3 Glasgow factors or a PMN-elastase ≥400 μg/l were assessed as having severe pancreatitis.

PMN-elastase measurement within 24 hours of admission was not superior to the Glasgow system as a prognostic indicator for acute pancreatitis in this series of patients. This was disappointing as success with this marker would imply simplicity assessment.

Effect of pancreatic enzyme supplementation on the management of acute pancreatitis

R V PATANKAR, R CHAND, C D JOHNSON (University Surgical Units, Southampton General Hospital, Southampton and Daphar Laboratories Ltd, Southampton) Earlier studies suggest that pancreatic enzymes may initiate feedback inhibition within the pancreas and when given in the convalescent phase improve exocrine function in patients with acute pancreatitis. Enzyme supplements may also reduce pain in chronic pancreatitis.

Our aim was to evaluate the effect of pancreatic enzymes in the management of acute pancreatitis. Twenty three patients (13 male, 10 female, age range 29–86) were entered into a double blind, prospectively randomised, placebo controlled study. Each subject received either placebo (n=10) or capsules containing protease 210 units BP, lipase 8000 units BP, and amylase 9000 units BP (n=9) for a time period ranging from 5–10 days depending on the severity of their disease. Daily pain scores were recorded using a visual analogue scale and analgesic requirements by a numerical method.

No statistically significant difference was found between the two groups in the daily pain scores or analgesic requirements, p=0.56. Median (range) hospital stay with placebo was 7 (5–10) and with pancreatic enzyme supplements was 8 (6–24), p=0.069.

In conclusion, we have found no evidence to support the use of pancreatic enzyme supplementes in the initial management of acute pancreatitis.

Patient selection and timing of dynamic computed tomography in acute pancreatitis

M LUCAROTTI*, J VIRJEJ†, D ALDERSON* (Departments of Surgery and Radiology, Bristol Royal Infirmary) Dynamic computed tomography is the most accurate method of determining the presence and extent of necrosis in acute pancreatitis. Debate exists, however, regarding patient selection and the timing of computed tomography. This study examines selection based on biochemical or clinical criteria, or both and the influence of delayed dynamic computed tomography performed 5–10 days after the onset of an attack.

One hundred and twenty patients with acute pancreatitis were studied. Dynamic computed tomography was done if any of the following were identified: biochemical criteria and the Glasgow (Glasgow criteria) in the first 24 hours, C reactive protein >120 mg/l in the first three days, failure of clinical resolution within seven days. Of 42 patients selected for scanning, five died from multisystem organ failure before day 5. There were no deaths or delayed complications in the 78 patients not selected for scanning. Predictive values of the selection criteria were:

<table>
<thead>
<tr>
<th>Computed tomography</th>
<th>Present</th>
<th>Absent</th>
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<tbody>
<tr>
<td>Glasgow criteria alone</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>CRP values alone</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Glasgow+CRP</td>
<td>12</td>
<td>0</td>
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<tr>
<td>Clinical alone</td>
<td>2</td>
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Delayed complications (pseudocyst, infection) occurred only in patients with necrosis, with two deaths. An at risk group can be identified for computed tomography on the basis of biochemical and clinical findings. The case for either routine or emergency dynamic computed tomography in acute pancreatitis seems unjustified.

Further characterisation of a new model of acute pancreatitis

I J FORMELA, J R NASH, A N KINGSMORTH (University Departments of Surgery and Pathology, Royal Liverpool University Hospital, Liverpool) Existing animal models of acute pancreatitis are well characterised but may not mimic the pathogenesis of the human disease. The aim of this study was to further characterise an ischaemic model of acute pancreatitis in the rat.

Acute pancreatitis was induced in male Wistar rats by retrograde infusion of 500 ul of 20 um diameter polylysine microspheres into a distal pancreatic artery. Control animals received a retrograde infusion of saline.

Histological changes occurred as early as six hours post induction as evidence by interstitial oedema, neutrophil infiltration, and focal necrosis and were progressive to 24 hour with extensive confluent acinar and fat necrosis. These changes in 30 animals, scored by a modification of the method described by Schmidt et al are reproducible, progressive, and similar to changes seen in human disease.

Serum amylase activities are raised at two hours (2500±500 U/l) control values 110±300 U/l becoming maximal at 24 hours 4500±400 U/l)
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Serum calcium values remained within the normal range.

Impairment of regional pancreatic blood flow in the rat by arteriolar microemobilisation leads to acute pancreatitis and the reproducible biochemical and histological changes induced suggest that this model is suitable for experimental therapeutic manipulation.


Interleukin-2 treatment improves survival in murine acute pancreatitis

P CURLEY, M NESTER, K COLLINS, M MENDEZ, I SPOSORSCHETZ, J MANNICK, M RODRICK (Department of Surgery, Brigham and Women’s hospital Boson, USA) We have recently shown reduced interleukin-2 (IL-2) production from isolated splenocytes in mice with acute pancreatitis induced by a choline deficient, ethionine supplemented diet. This is associated with a 90-100% death rate after an endotoxin challenge, compared with 0% death in normal animals. The hypothesis tested in this experiment was that administration of exogenous IL-2 could abrogate the reduction in IL-2 production and improve survival in acute pancreatitis.

Two groups of female Swiss-Webster mice (20-25 g weight) were fed a choline deficient diet supplemented with 0.5% dl ethionine (AE mice). One group received 15,000 units IL-2 intraperitoneally per day for five days (AP/IL-2) and another group received placebo injections (AP/vehicle). A third group of mice were fed normal laboratory chow and received vehicle injections (N/vehicle). Mice were killed on day 10 and splenic mononuclear cell in vitro IL-2 production measured using a bioassay specific for IL-2. Three further groups of mice received intraperitoneal endotoxin (0.25 mg/kg) on day 10, and five day survival observed.

Exogenous IL-2 can improve survival after septic challenge in an animal model of acute pancreatitis and is associated with upregulation of mononuclear IL-2 production.

A prospective, multicentre, controlled, randomised trial of intraperitoneal trasylol treatment for acute pancreatitis

M LARVIN*, C WILSON†, D HEATH*, D ALEXANDER*, M J McMATH*, C W IMRE† (University Department of Surgery*, The General Infirmary at Leeds, and Department of Surgery*, The Royal Infirmary, Glasgow) Fatal acute pancreatitis (AP) is often associated with multiple organ system failure (MOSF). Agents which may start MOSF accumulate within peripectoneal fat, due to free protease activity. Peritoneal lavage removes exudate, but causes fluid sequestration, protein loss, and respiratory embarrassment. Adding an anti-protease may improve efficiency while reducing volume. Pharmacodynamic studies showed a suitable regimen, administering 5X10^6 kiu intraperitoneal aprotinin (IPA) in 1000 ml saline, repeated after eight hours. The study involved 23 hospitals, and compared standard conservative management (SCM) with IPA plus SCM. Seven hundred and ten patients were assessed (369 males:341 females; median age 57 years; aetiology: gallstones 34%, alcohol 19%). Patients were randomised if aged 16-84 years; history <72 hours; no contraindication to IPA. Obviously mild AP (no peritonism/ hypoxia/hypotension) was excluded. Complications were defined by predetermined criteria, and MOSF monitored by APACHE-II scores. Of 208 patients randomised, three refused consent, two cunnulations failed, leaving 96 IPA and 107 SCM patients of comparable age, sex, cause, Imrie/APACHE-II scores.

There were no significant differences in death, major morbidity, MOSF, serial APACHE-II, or hospital stay, even when stratified for severity by Imrie or APACHE-II systems. Given the statistical power of the study (p>0.90 and a=0.05), IPA does not seem to be efficacious.

The effects of major surgery and nutritional support on pancreatic function and morphology in critically ill gastroenterological patients

P M SAGAR, P POON, D WAI, C J MITCHELL, J MACFIE (Scarborough Hospital) We have investigated the effects upon pancreatic exocrine function in similar groups having major surgery (n=18), parenteral (TPN, n=18), and enteral nutrition (EN, n=16). Pancreatic exocrine function was measured using the PABA test (IGN-benzoyl-L-tyrosyl PABA given and 3 hour serum PABA analysed). Pancreatic morphology was assessed by real time ultrasound to calculate a pancreatic size (maximum diameter of head x body). Serial measurements were performed in all patients on entry into the study and at 7 and 14 days postoperatively or during feeding.

The compartment syndrome of chronic pancreatitis

N D KARANJIA, A L WIDDESON, H A REBER (Surgical VAMC and UCLA, Los Angeles, California, USA) We showed that pancreatic blood flow (PBF) was decreased in cats with obstructive chronic pancreatitis (CP) and that PBF decreased even further during secretory stimulation. Normally it increased. Here we studied the effect of decompression of the main pancreatic duct (MPD) on PBF. Anaesthetised cats had the MPD near the duodenum narrowed by 75% to create obstructive CP. In five weeks the dilated MPD was cannulated in the tail of the pancreas with a platinum electrode. Normal cats were studied in the same way. In some of the CP cats (Decomp CP), the MPD was opened acutely in the head of the pancreas and allowed to drain freely. PBF (ml/min/100 g) was measured under basal and maximally stimulated conditions.

There was no significant difference in the pancreatic size index between the three groups. Serum PABA values were similar in the three groups at entry and unchanged in the TPN and EN groups. There was, however, a significant and progressive decrease at 7 and 14 days postoperatively in the surgical group. Adjuvant nutritional support preserves pancreatic exocrine function regardless of the route of administration. Major surgery, however, causes a dramatic reduction in exocrine func-

tion. This provides additional evidence to justify postoperative nutritional support.
of CP, and the therapeutic effect of duct drainage.

Mode of digest release into the magnetic field significantly affects immunomagnetic islet purification

G S M ROBERTSON, J DAVIES, J J CHAMBERLAIN, P R F BELL, R J JAMES, N J LONDON (Department of Surgery, Clinical Sciences Building, Leicester Royal Infirmary, Leicester) After collagenase digestion of the pancreas, the results of islet purification with density gradient centrifugation are often disappointing. We hope to overcome this on a large scale using a panel of monoclonal antibodies to all the non-islet components (ancini, ducts, vessels, and lymph nodes) of the pancreas, coupled to magnetic M-450 Dynabeads.

One problem encountered during separation of the magnetically labelled non-islet tissue is the trapping of islets in the meshwork of magnetised beads and attached non-islet tissue. We have done a careful study to determine the optimal method of passing the pancreatic digest through the magnetic field, assaying the percent of acinar tissue (amylsace) and islets insulin trapped.

Slow release of the digest from a narrow outlet into tissue culture medium, allowing it to drift under gravity through the magnetic field, gave optimal acinar removal (median of 94.5%, range 86.9-97.3%) with minimal islet losses.

In conclusion, effective islet purification can be achieved by modifying immunomagnetic cell separation procedures. This will allow increased yields of islets from single donor pancreata, increasing the chances of successful islet transplantation.

Is diagnostic endoscopic retrograde pancreatography (ERP) now a necessary investigation?

N SALIAN, T DUGGORY, D WAI, J G GLAVES, L MACFIE, C J MITCHELL (Combined Gastroenterology Service and Department of Radiology, Scarborough Hospital, Scarborough, North Yorks) Improvised instrumentation and technical expertise have increased the diagnostic accuracy of pancreatic ultrasound (US) to an extent that we felt that ERP rarely provided additional diagnostic information. We therefore evaluated our routine US and ERP service prospectively in 100 patients (51 men and 49 women, aged 17-88 years) in whom a good quality US and ERP were obtained. Forty one patients presented with abdominal pain and 36 were jaundiced. Sixteen patients were investigated after asymptomatic relapse of chronic or recurrent pancreatitis. Seven patients presented with weight loss. The final diagnoses were pancreatic carcinoma (22 patients), chronic pancreatitis (23), relapsing pancreatitis (8), and pancreas divisum (7). Forty patients had no pancreatic disease.

Ultrasound correctly diagnosed most patients (73) and ERP was merely confirmatory but did provide additional information in 14 (20%). The US diagnosis, however, was wrong in 22 of 66 patients where ERP was correct. Half of these occurred in pancreatitis, especially when localised or sidebranch changes were present. Pancreas divisum was not detected and five US mass lesions were not confirmed. In four patients the correctly diagnosed carcinoma was (2) or pancreatitis undetected by ERP.

Despite improvements in pancreatic ultrasound ERP remains a more sensitive investigation for diagnosing pancreatitis, detecting pancreatic divisum and often provides important additional information.

Insulinoma: accurate localisation by selective angiography and surgical management

J G GEOGHEGAN, M P N LEWIS, E R T C OWEN, J A LYNN, R C N WILLIAMSON (Departments of Endocrine and Hepatopancreatobiliary Surgery, Hammersmith Hospital, Du Cane Road, London) Localisation of an insulinoma remains the key to successful surgical management. From 1976 to 1992 33 patients with a mean age of 42 years (19 female, 14 male) were referred with suspected insulinoma. The diagnosis was confirmed by the finding of hypoglycaemia with inappropriate hyperinsulinaemia during super- vised fasting. Twenty seven patients had an adenoma, two had islet hyperplasia, two had carcinoma, and two patients had negative exploration. Selective visceral angiography (SVA) correctly localised all 27 adenomas and the two carcinomas, with two false positives. In both patients with hyperplasia SVA showed a solitary lesion only. Computed tomography identified the lesion in only six of 24 (25%). One patient was lost to follow-up and one had localisation alone. Eighteen tumours were enucleated and 13, including two patients with hyperplasia, were managed by distal pancreatectomy (with splenic preservation in three). There were no operative deaths. Nine patients (28%) had complications (two subphrenic collections, five wound infections, one acute pancreatitis, one pulmonary embolism). SVA localised 100% of insulinomas but did not identify islet cell hyperplasia. Operation successfully relieved symptoms in 94% of patients with no death and low morbidity.

Adjuvant radiochemotherapy after resection of pancreatic adenocarcinoma: preliminary results

J P NEOPTOLEMOS (Department of Surgery, Dudley Road Hospital, Birmingham) Resection for pancreatic cancer is associated with a five year actuarial rate (YASR) of 5-15%. Adjuvant treatment after resection of these lesions has only been one study published. The N American GITSG phase III study reported an improve- ment after postoperative radiotherapy and 5-FU iv weekly in 20 patients with pancreatic cancer (43% 2 YASR vs 18% in control arm). The GITSG protocol was repeated in 27 patients with adenocarcinoma of the pancreas (n=23) or peripancreatic adenocarcinoma (n=4; one with resected solitary liver meta- stasis). There were 10 women and 17 men with a mean age of 59-4 (range 40-76) years. A standard Kausch-Whipples operation was performed in 11, 13 had a pylorus preserving head resection, two had total, and one had a distal pancreatectomy. Lymph node metastases were present in 17 cases; the histological grade was 1-8, 2-11, and 3-8. The radiotherapy was well tolerated with only one related complica- tion. There was no significant drug toxicity. At a median follow up of 12 (range 3-36) months the 2 YASR was 30%; 14 patients were dead, 12 alive, and one lost to follow up.

These results show that postoperative radiochemotherapy after resection is worthwhile. The 2 YASR was intermediate between the treated and control arms of the GITSG study. A larger phase III trial is necessary to establish the efficacy of the GITSG protocol.

The RBl tumour suppressor gene in human pancreatic cancer

C M BARTON, A B MACIE, N R LEMOINE (IGRF Oncology Group, Hammersmith Hospital, Du Cane Road, London) The Kirsten ras gene is mutated at codon 12 in over 75% of cases of pancreatic adenocarcinoma but there is abundant evidence to suggest that mutant ras alone is not sufficient to fully transform human epithelial cells and that at least one other genetic event is necessary. Loss of inactivation of one or more tumour suppressor genes is a likely candidate for the cooperating event. We present the results of our investigations into the retinoblastoma susceptibility gene RB1.

A panel of 14 pancreatic cancer cell lines was screened for abnormalities in the 27 exons and promoter region of RB1 using the technique of single strand conformation polymorphism analysis (SSCP). Two cell lines showed devia- tions from the wild type pattern suggestive of mutations (Coll-357 in exon 2, Pitu-2 in exon 9) and one cell line (AsPC-1) had missing bands in exon 12 and 13. This may reflect the adjacent exon 25 suggesting a possible deletion spanning more than one exon. RB protein expression is being assessed in these cell lines by immuno- precipitation. A series of tumour/normal pairs is currently being screened for loss of heterozygosity at the RB1 locus by polymerase chain reaction amplification of an intragenic microsatellite repeat. Evidence of allele loss was detected in 2/23 pancreatic carcinomas and 0/4 amputary tumours. These results suggest that abnormalities of RB1 may occur in a minority of pancreatic cancers.

Detection of K ras oncogene mutations in pancreatic juice – a potential diagnostic test for pancreatic adenocarcinoma

J FAWCETT*, M RHOADES, J BRITTON (Department of Surgery and Molecular Oncology, John Radcliffe, Oxford, and Department of Surgery, Frenchay Hospital, Bristol) Over 90% of pancreatic adenocarcinomas harbour mutations in the K ras protooncogene, the highest incidence of this abnormality in any human cancer. If this mutation could be easily detected in clinical material such as pancreatic juice it might provide the basis for a diagnostic test to detect the development of the polymerase chain reaction (PCR) has made it possible to amplify specific regions of the genome to look for the presence of sequence mutations. Malignant cells can sometimes be detected cytologically in the exocrine secretions from patients with pancreatic cancer and it is therefore theoretically possible that K ras mutations can also be shown in DNA amplified from pancreatico- biliary secretions. We have investigated the specificity of amplifying DNA from pancreatic juice obtained at ERCF as a first step in looking for genetic abnormalities.

The first exon of the K ras gene was success- fully amplified from various cell lines with as few as 100 cells. The same primers were then used to study pancreatic juice collected from seven patients, two of whom had cancer. To amplify DNA from these samples it was neces- sary to treat with Siplo-1 and proteinase K followed by phenol extraction and salt precipitation of DNA. With this method it was possible to amplify exon 1 in all specimens. Further work is underway to detect K ras codon 12 and 13 mutations in these specimens.

Detection of K ras oncogene mutations in pancreatic juice may provide the basis for a diagnostic test for pancreatic adenocarcinoma.